- **Hypertriglyceridemia** may be secondary to diet, obesity, excess alcohol intake, diabetes mellitus, hypothyroidism, uremia, dysproteinemias, β-adrenergic antagonists, estrogen, oral contraceptive drugs, retinoids, antiretroviral medications, tacrolimus, and sirolimus.
  - Triglyceride levels >400 mg/dL are often associated with an underlying primary disorder. Primary hypertriglyceridemia can be due to FCHL or familial hypertriglyceridemia (FHTG).
  - Families with familial hypertriglyceridemia have multiple members with elevated triglyceride levels due to increased VLDL levels. FHTG appears to be an autosomal dominant disorder without a clearly defined molecular basis. Families may show less pronounced risk of CHD than those with FCHL.
- **Dysbetalipoproteinemia** (type III hyperlipoproteinemia) is a rare (approximately 1 in 5,000) disorder caused by an abnormality of apoprotein E, a protein on the surface of VLDL and other lipoproteins, which is important in the uptake of remnant particles by cell surface receptors. Cholesterol-enriched VLDL (β-VLDL), an atherogenic particle, accumulates.
  - Both cholesterol and triglycerides are elevated.
  - Isoelectric focusing, which shows an abnormal apoprotein E pattern, can be confirmed by specific genotyping. Patients may have palmar or tuberoeruptive xanthomas, and there is increased risk of vascular disease. Patients with this disorder may respond well to diet and weight loss.
- **Hyperchylomicronemia** is diagnosed by the presence of a chylomicron layer when plasma is centrifuged or when chylomicrons float to the top of plasma that has been refrigerated overnight.
  - Chylomicrons can be seen when triglyceride levels are in excess of 1,000 mg/dL. The patient may have rare syndromes involving absence of lipoprotein lipase activity or absent apoprotein CII (a cofactor of lipoprotein lipase). Chylomicrons alone may be increased, as in lipoprotein lipase deficiency, or both VLDL and chylomicrons may be elevated.
  - Total cholesterol levels are often markedly elevated because of the presence of large numbers of VLDL particles that contain cholesterol as well as triglycerides. Patients with primary hypertriglyceridemia, FCHL, or dysbetalipoproteinemia may develop hyperchylomicronemia in the presence of excessive dietary fat intake, uncontrolled diabetes, alcohol excess, obesity, or other secondary causes of hyperlipidemia.
  - The chylomicronemia syndrome may include abdominal pain, hepatomegaly, splenomegaly, eruptive xanthomas, lipemia retinalis, and pancreatitis. Memory loss, paresthesias, and peripheral neuropathy can also occur.
- **Family members** of patients with hyperlipidemia should be screened to facilitate diagnosis of primary hyperlipidemias as well as to identify other patients in need of treatment.
- **Secondary causes of hyperlipidemia** include diet, hypothyroidism, diabetes mellitus, nephrotic syndrome, chronic renal failure, and dysproteinemia. Certain drugs can have effects on lipids. Thiazide diuretics, β-adrenergic antagonists (particularly less selective ones), glucocorticoids, estrogens, progestins, retinoids, anabolic steroids, protease inhibitors, and alcohol have variable effects on cholesterol, triglycerides, and HDL cholesterol. Treatment of diabetes mellitus with good control of blood sugars is particularly important if reasonable control of hypertriglyceridemia is to be achieved.
- **Low HDL-C levels** (<40 mg/dL) may be due to a genetic disorder or to secondary causes.
  - ***Primary disorders*** include familial hypoalphalipoproteinemia, primary hypertriglyceridemias, and rare disorders such as fish-eye disease, Tangier disease, and lecithin-cholesterol-acyl transferase (LCAT) deficiency.
  - ***Secondary causes*** of low HDL-C levels include cigarette smoking, obesity, lack of exercise, androgens, some progestational agents, anabolic steroids, β-adrenergic antagonists, and hypertriglyceridemia.
- **The metabolic syndrome** is a secondary target of risk reduction therapy. It is a constellation of factors including abdominal obesity, insulin resistance or diabetes, hypertension, and atherogenic lipid profile (elevated triglyceride levels; small, dense LDL; low HDL).

- Patients are considered to have the metabolic syndrome if they have three of the following:
  - Abdominal obesity: waist circumference >102 cm in men and 88 cm in women
  - Triglycerides ≥150 mg/dL
  - HDL-C <40 mg/dL in men and 50 mg/dL in women
  - Blood pressure ≥130/85 mm Hg
  - Fasting glucose ≥100 mg/dL
- **Elevated levels of lipoprotein (a) above 30 mg/dL** are associated with increased risk of atherosclerotic cardiovascular disease. Measurement of lipoprotein (a) may be useful in assessing risk in patients with few risk factors but with a strong family history of premature atherosclerosis. Lipoprotein (a) responds poorly to both nonpharmacologic and drug therapy. There can be modest reductions with niacin. The primary approach to therapy is reduction of LDL-C.

Treatment

- Patients who have **coronary disease** should have LDL-C levels reduced to 100 mg/dL or less (<70 mg/dL in very-high-risk patients).
  - Therapy should begin during hospitalization for an acute coronary event if patients are not already being treated.
  - Patients with coronary disease should be treated with the NCEP-TLC diet, which restricts saturated fat to 7% of total calories and daily cholesterol intake to <200 mg. Patients should see a dietitian for assistance in making diet changes. Patients with elevated triglycerides need to restrict simple sugars and alcohol as well.
- LDL-C can be lowered with the HMG-CoA reductase inhibitors (statins): lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and rosuvastatin; the bile acid sequestrant drugs cholestyramine, colestipol, and colesevelam; the cholesterol absorption inhibitor ezetimibe; and nicotinic acid (niacin).
  - The **HMG-CoA reductase inhibitors** lower LDL cholesterol well in most patients. These are the drugs of choice for lowering LDL for secondary prevention. LDL cholesterol can drop by 20%–60% depending on the drug and dosage. HDL may increase by up to 15% and triglycerides decrease by up to 30%.
    - All the statins are similar in mechanism of actions and side effects.
    - Atorvastatin and rosuvastatin have half-lives of approximately 13 hours and 20 hours, respectively. The other reductase inhibitors have half-lives of approximately 2–3 hours. Extended-release formulations of lovastatin and fluvastatin have longer half-lives than their counterparts. Lovastatin is best given with food, usually with evening meal; pravastatin, simvastatin, and fluvastatin can be administered without food, preferably in the evening.
    - Side effects occur infrequently (approximately 5%–10% of patients) and most commonly include mild gastrointestinal discomfort and myalgias.
    - **Liver function tests** should be monitored every 6–12 weeks initially and then every 6–12 months (or according to package inserts). About 1% of patients will have transaminase elevations to greater than three times the upper limit of normal; the transaminase elevation will often decrease while the patient continues on the statin. A common cause of this problem is fatty liver, which responds to small amounts of weight loss. If transaminases continue to be elevated, changing to a different statin may be helpful. Other drugs or conditions may contribute to elevated transaminases, such as increased alcohol intake.
    - **Myopathy** may occur in up to 10% of patients. Patients may have complaints of muscle cramps, aching, or weakness. Myopathy has been reported more often when the reductase inhibitors are combined with fibric acid derivatives, cyclosporine, niacin, and erythromycin. Patients with myalgias due to statins may have normal or elevated CK levels. Symptoms usually improve within a few days after the drug is discontinued. Some patients who have myalgias with one statin may be able to tolerate another statin. The myalgias may also be dose related in some patients.

- **Rhabdomyolysis** is a rare complication of statin use. It is more likely to occur in elderly or debilitated patients, individuals with renal or congestive heart failure, or patients on medications that affect the metabolism of the statins, including fibric acid derivatives (especially gemfibrozil), cyclosporine, macrolide antibiotics, or drugs with significant cytochrome P-450 metabolism such as itraconazole.[10]

- **Bile acid sequestrant resins** lower LDL by 15%–30%. Because the resins can raise triglycerides, they should not be used as monotherapy in patients with triglycerides above 250 mg/dL. Usual dosages are 4–20 g/d of cholestyramine or colestipol. Up to 24 g of cholestyramine or 30 g of colestipol may be used.
  - **Cholestyramine** and **colestipol** are available in powder form, in bulk, or in single-dose packets. Colestipol is also available in 1-g tablets. Once- or twice-daily dosing close to meals is desirable. A single daily dose of up to 8–12 g may be useful to fit the resin into a medication schedule. Resins can be combined with nicotinic acid or reductase inhibitors to treat patients with severe elevations of LDL cholesterol where greater reductions of LDL are required.
  - **Colesevelam** is another bile acid–binding drug. It is available in 625-mg tablets with a recommended dose of six tablets per day and a maximum dose of seven tablets per day. LDL cholesterol reduction is 15%–18%. Interactions with other drugs and gastrointestinal side effects may be less frequent than with the older resins. The addition of bile acid–binding drugs to statins can produce additional reduction of LDL levels that are needed to get to goal in some patients.
  - The most common side effects of the resins are bloating, hard stools, and constipation. Initiation of therapy with low doses, patient education, and use of stool softeners or psyllium can increase compliance. Many patients like the idea of taking a medication that is not absorbed. Patients with severe constipation and very complicated drug regimens are not usually good candidates for resin therapy. Side effects are generally less with colesevelam than with the older resins. Other medications must be taken 1 hour before or 4 hours after the cholestyramine or colestipol.

- **Ezetimibe** is a cholesterol absorption inhibitor. It blocks the absorption of cholesterol at the level of the enterocyte. LDL cholesterol levels can decrease by about 20%. The dose is 10 mg daily, and it is not affected by food. Ezetimibe can be used alone or in combination with statins.
  - The addition of ezetimibe to a given dose of a statin may produce additional lowering of LDL by 20% or more.
  - Side effects include diarrhea and myalgias.
  - Liver enzyme elevations can occur with the combination of ezetimibe and statins, and transaminases should be monitored with the combination as they would be with the statins.
  - Fixed-dose simvastatin/ezetimibe combination tablets are available and can be considered in patients who are using this combination.

- **Nicotinic acid** or **niacin** can lower triglycerides, raise HDL, and lower LDL in higher doses. It is particularly useful in combined hyperlipidemia and in patients with low levels of HDL. Niacin requires extensive patient education because of the flushing and other side effects that can occur.
  - To initiate therapy with nicotinic acid, patients should begin taking 100 mg/d for 2–3 days, then increase to 100 mg tid for 1 week, then 200 mg tid the second week, and 300 mg tid the third week, and repeat lipids; serum chemistries should be obtained after another 3 weeks while patients remain on 300 mg tid. The dose can gradually be increased to the highest dose the patient can tolerate that produces desired results, up to 3,000 mg/d. Patients should report any nausea or increased fatigue as these may be signs of toxicity; liver function tests should be measured and the dose decreased if these are elevated. For patients on higher doses, 500-mg non–time-release tablets are available from several manufacturers. A prescription-only, extended-release formulation can be given once a day at bedtime; significant liver toxicity was not reported at doses up to 2,000 mg/d in clinical trials. Thus, the maximum dose is 2,000 mg/d. The initial dose is 500 mg at bedtime. The dose can be increased by 500 mg at 4-week intervals up to the

maximum dose. The entire dose should be given at bedtime, and this preparation should not be combined with any other niacin preparations.

- **Adverse effects.** Some over-the-counter sustained-release preparations have been associated with severe liver toxicity; crystalline or non–time-release preparations should be used. Flushing can be decreased by starting with low doses, use of aspirin before each dose, and having the patient take nicotinic acid with meals. Uric acid, blood glucose, and serum transaminases should be monitored every 6–8 weeks during the titration phase. Nicotinic acid should be avoided in patients with a history of gout, active peptic ulcer disease, and liver disease. Diabetic patients should only use niacin if they have hemoglobin A_{1c} levels of approximately 7% or less and should monitor blood sugars closely.

- **Hypertriglyceridemia** usually responds to a combined approach using nonpharmacologic and drug therapy.
  - Patients should be instructed to decrease their intake of alcohol and simple sugars and to exercise regularly. Some patients who markedly increase their carbohydrate intake will have increases in triglyceride levels. Hypertriglyceridemic patients should generally not be on diets with fat content <25% of calories, except for patients with the chylomicronemia syndrome. The response to very-low-fat diets (i.e., 10% of calories from fat) may be disappointing in patients with impaired glucose tolerance unless the diet is sufficiently hypocaloric. Very-high-carbohydrate diets that are isocaloric may lead to poor glycemic control and increased triglyceride levels. A particular problem is a high intake of nonfat desserts leading to increased calories in an otherwise low-fat diet. Modest amounts of weight loss can be extremely helpful. In addition, patients with diabetes, especially those with very high triglyceride levels, should have good glycemic control.
    - Omega-3 fatty acids, found in fish oils, can help reduce triglyceride levels. Fish oil capsules containing the long-chain fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can be used as an adjunct to other therapies in patients with hypertriglyceridemia. At doses of 3–6 g/d of eicosapentaenoic acid and docosahexaenoic acid, triglycerides may decrease by up to 30%. The major drawbacks to high doses of these fatty acids are large numbers of pills to be taken, eructation, and occasional diarrhea. They have a mild antiplatelet effect, which may be of concern in patients who are receiving warfarin or antiplatelet drugs. A prescription-only omega-3 preparation is available. Four tablets contain about 3.6 g of omega-3 acid ethyl esters and can lower triglycerides by 20%–30%.
  - **Drug therapy**
    - Patients with triglycerides of 400 mg/dL or less and elevated LDL cholesterol levels may respond adequately to a statin added to nonpharmacologic measures.
    - If the triglycerides are above 400 mg/dL despite adequate dietary modifications and exercise, the choice of medication could include a statin at higher doses, gemfibrozil, fenofibrate, niacin, or omega-3 fatty acids.
    - For patients with triglycerides over 1,000 mg/dL, fibrates and niacin are the drugs of choice. If LDL cholesterol levels remain high after the triglycerides are lowered, combination therapy can be considered.
    - Combination therapy of niacin and a statin or fibrate and a statin may increase the risk of **myopathy** including **rhabdomyolysis.** The risk is less with a statin–niacin combination. The combination of a fibrate and statin should be avoided in patients with renal insufficiency, congestive heart failure, severe debility, or other conditions, which may affect the metabolism of medications. Patients whose triglycerides remain above 200 mg/dL should have non-HDL cholesterol evaluated as a secondary goal of therapy. If non-HDL cholesterol is not at goal, therapeutic lifestyle changes should be emphasized. The dose of statin can be increased or a second medication such as ezetimibe can be added. Gemfibrozil and fenofibrate are the fibric acid derivatives that are available in the United States.
    - The usual dose of **gemfibrozil** is 600 mg bid before meals. Triglyceride levels are usually reduced by 30%–50%. The drug should not be used in patients with very low creatinine clearances. Abdominal pain and nausea are the most common side effects. The incidence of gallstones is increased in patients who are receiving

the fibric acid derivatives due to increased cholesterol content of bile. Patients on warfarin need to have their INR monitored closely after they start taking gemfibrozil.

- The use of **fenofibrate** is similar to that of gemfibrozil. Fenofibrate is available in several different strengths, including 48- and 145-mg tablets; 54- and 160-mg tablets; 67-, 134-, and 200-mg capsules; and 43-, 87-, and 130-mg capsules. Fenofibrate can be given once a day with a meal. Although the starting dosages are the lower strengths, many patients require the full dose of 145 or 160 mg/d. However, a lower dose should be used in patients with renal insufficiency. It can be given once a day with a meal. Side effects, which occur in 5%–10% of patients, are primarily mild gastrointestinal discomfort and, less frequently, rash and pruritus. Increased transaminases occur in about 5% of patients and return to normal when the drug is discontinued. Infrequently, myalgias and increased CPK have been reported. In addition to its use for lowering triglycerides, fenofibrate may also be useful in some patients with combined hyperlipidemia who have moderately elevated LDL cholesterol levels and high triglycerides.
- Drugs such as **estrogen, retinoids,** and **thiazides** may contribute to hypertriglyceridemia. The use of transdermal estrogen instead of oral estrogen preparations can lead to significant decreases in triglyceride levels in women who are receiving postmenopausal HRT. Oral estrogen preparations should be avoided in women with triglyceride levels above 500 mg/dL.

- The **chylomicronemia syndrome** requires a diet that is very low in total fat. Patients with triglycerides above 2,000 mg/dL should initiate a diet with <10% of total calories as fat. It may be possible to gradually increase the fat content as the triglyceride level falls to <500 mg/dL. Primary lipoprotein lipase deficiency is treated with fat restriction and does not respond to drug therapy.
- **The metabolic syndrome** is a secondary target of risk reduction therapy. Weight control and increased physical activity are important in the treatment of the metabolic syndrome. Other risk factors such as hypertension should also be treated. Elevated triglycerides or low HDL, or both, should be treated once the LDL goal has been reached.
- **Low HDL cholesterol** levels are associated with an increased risk of cardiovascular disease. Attention should be given to factors that lower HDL, such as cigarette smoking and certain medications such as β-adrenergic–blocking agents, androgenic compounds, and progestins. Nonpharmacologic therapy such as exercise, weight loss, and smoking cessation should be stressed. Niacin is the most effective agent for increasing HDL. Some increase (approximately 10%–20%) can occur with fibrates, but generally only in patients with elevated triglycerides. Once patients have reached LDL cholesterol goals, the addition of niacin may be useful to raise HDL cholesterol levels in suitable patients.

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United States Patent [19]
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[54] **NOVEL DOSAGE FORM OF FENOFIBRATE**

[75] Inventors: **Bernard Curtet,** Marsanny la Cote; **Eric Teillaud,** Talant; **Philippe Reginault,** Fontaine les Dijon, all of France

[73] Assignee: **Fournier Innovation et Synergie,** Paris, France

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[52] **U.S. Cl.** **424/456;** 424/452; 424/458
[58] **Field of Search** 424/456, 452, 458

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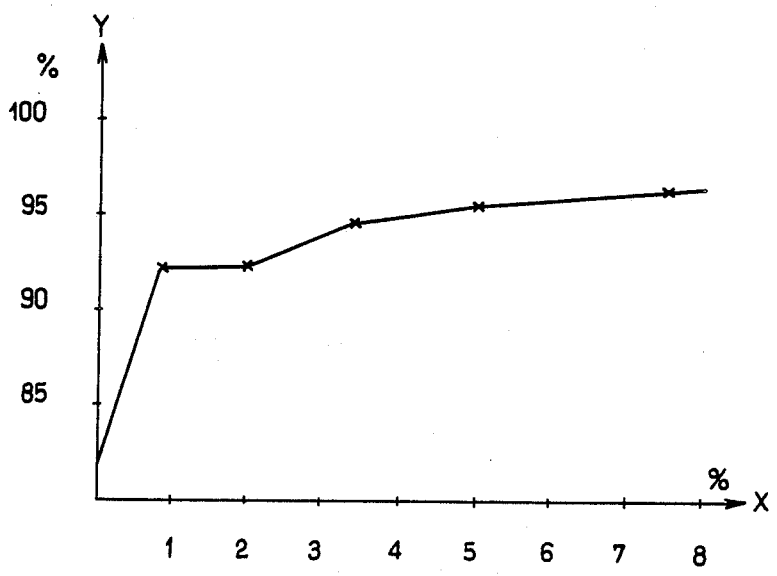
Primary Examiner—Ellis P. Robinson
Assistant Examiner—Leon R. Horne
Attorney, Agent, or Firm—Fleit, Jacobson, Cohn, Price, Holman & Stern

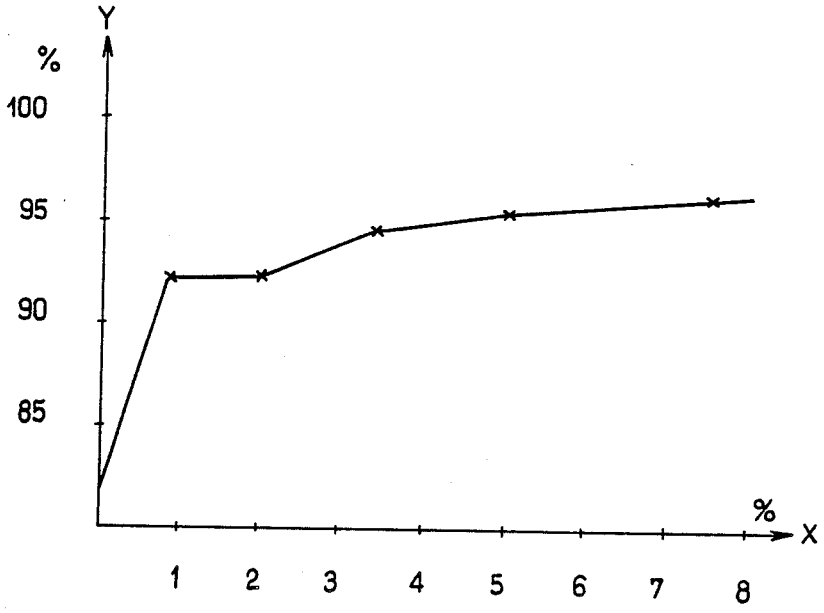
[57] **ABSTRACT**

The present invention relates to a novel dosage form of fenofibrate containing fenofibrate and a solid surfactant which have been co-micronized.

It also relates to the method for the preparation of this dosage form and its use for improving the bioavailabity in vivo.

12 Claims, 1 Drawing Sheet

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NOVEL DOSAGE FORM OF FENOFIBRATE

The present invention relates to a novel dosage form of fenofibrate. It relates more precisely to a therapeutic composition containing fenofibrate and ensuring an improved bioavailability, and to a method for the preparation of this composition.

Fenofibrate (international common name), which is recommended in the treatment of hyperlipidemia and hypercholesterolemia, corresponds to the nomenclature isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropionate. The customary adult dosage is three gelatin capsules per day, each containing 100 mg of fenofibrate.

For the patient's comfort, it is advantageous to try and find a dosage form which has to be taken only once a day and whose psychological effect is identical to that obtained when multiple doses are taken. A gelatin capsule containing 300 mg of fenofibrate has therefore been proposed, the dosage recommended in this case being only one administration per day.

However, it is possible to try and improve the dosage form still further. It is known, in fact, that the bioavailability of fenofibrate is not equal to 100%. It is therefore desirable to develop a dosage form in which the bioavailability of the fenofibrate is improved and which can be administered only once a day.

It is known that the micronization of an active principle is capable of improving the dissolution of the said active principle in vivo, and hence its bioavailability. It is also known that the addition of a surfactant excipient to a formulation of an active principle is capable of improving the absorption and consequently the bioavailability of the said active principle.

It has now been discovered that the co-micronization of fenofibrate and a solid surfactant (i.e. the micronization of an intimate mixture of fenofibrate and a solid surfactant) makes it possible to improve the bioavailability of the fenofibrate to a significantly greater extent than that which would be achieved either by adding a surfactant, or by micronizing the fenofibrate on its own, or by intimately mixing the separately micronized fenofibrate and surfactant.

The present invention therefore proposes a novel therapeutic composition, presented in the form of gelatin capsules, which is useful especially in the oral treatment of hyperlipidemia and hypercholesterolemia, the said composition containing fenofibrate and a solid surfactant which have been co-micronized.

The recommended amount of fenofibrate is about 200 mg per therapeutic unit.

The surfactant will be selected from solid surfactants so that it can be co-micronized with the fenofibrate. An alkali metal sulfate of lauryl alcohol, for example sodium lauryl-sulfate (alternative name: sodium dodecyl-sulfate), will be preferred. The recommended amount of sodium lauryl-sulfate will be between 0.5% and 7% by weight, relative to the total weight of the formulation. The weight ratio surfactant/fenofibrate will advantageously be between about 0.75/100 and 10.5/100.

The co-micronization of the fenofibrate and the solid surfactant will advantageously be carried out in an accelerated air-jet mill until the powder obtained is such that the mean particle size is less than 15 μm, preferably less than 10 μm and particularly preferably less than 5 μm.

To obtain a powder which can be formulated into gelatin capsules, conventional filling, dispersing and flow-enhancing excipients, for example lactose, starch, polyvinylpyrrolidone and magnesium stearate, may be added to the co-micronizate of fenofibrate and solid surfactant.

According to the invention, a method for the preparation of a therapeutic composition containing fenofibrate and a solid surfactant is recommended which comprises:

(i) intimately mixing and then co-micronizing the fenofibrate and the solid surfactant,

(ii) adding lactose and starch to the mixture obtained,

(iii) converting the whole to granules in the presence of water,

(iv) drying the granules until they contain no more than 1% of water,

(v) grading the granules,

(vi) adding polyvinylpyrrolidone and magnesium stearate to the graded granules, and

(vii) filling gelatin capsules with the mixture obtained in stage (vi).

The invention will be understood more clearly from the description of the Preparative Examples which follow and from the description of the results obtained in comparative tests, which show that the invention is non-obvious.

PREPARATION I

For 100,000 gelatin capsules, each weighing 350 mg and containing 200 mg of fenofibrate, the amounts of products used are as follows:

fenofibrate	20.0 kg
sodium lauryl-sulfate	0.7 kg
α-lactose monohydrate	10.1 kg
pregelatinized starch	3.0 kg
crosslinked polyvinyl-pyrrolidone	0.7 kg
magnesium stearate	0.5 kg

The fenofibrate/sodium lauryl-sulfate mixture is co-micronized in an air-jet micronizer to give a powder with a median partizle size of 3 μm. The lactose and the starch are then added to this powder and the whole is converted to granules in the presence of 8.9% of distilled water, relative to the total weight of the mixture. The granules obtained in this way are dried for one day at 50° C. and then graded so as to retain only the particles with sizes less than or equal to 1000 μm. The polyvinylpyrrolidone and the magnesium stearate are then added and the whole is mixed until homogeneous. The powder obtained is used to fill size 1 gelatin capsules on an automatic machine with the compression set to a maximum of 150N.

PREPARATION II

The procedure indicated in Preparation I is followed using a fenofibrate/sodium lauryl-sulfate mixture with a median particle size of 6–7 μm.

PREPARATION III

For 100,000 size 1 gelatin capsules, each weighing 297 mg and containing 200 mg of active principle, the amounts of products are as follows:

fenofibrate	20.0 kg
sodium lauryl-sulfate	0.3 kg
α-lactose monohydrate	6.8 kg
pregelatinized starch	1.5 kg

-continued

crosslinked polyvinyl-pyrrolidone	0.6 kg
magnesium stearate	0.5 kg

The procedure is analogous to that used for Preparation I, the co-micronization of the fenofibrate/sodium lauryl-sulfate mixture being such that the median particle size is 6–7 μm and the granulation being carried out in the presence of 10% of distilled water, relative to the weight of the fenofibrate/sodium lauryl-sulfate/lactose/starch mixture.

PREPARATION IV

Following a procedure analogous to that described in Preparation I, using a co-micronized mixture of fenofibrate and sodium lauryl-sulfate with a median particle size of 6–7 μm, the formulations collated in Table I below were prepared:

TABLE I

COMPOSITION (in mg) PER GELATIN CAPSULE						
	FORMULATION					
INGREDIENT	A	B	C	D	E	F
Fenofibrate	200	200	200	200	200	200
Na lauryl-sulfate	0	3	7	12	17.5	26.5
Lactose	108	105	101	95	90.5	83.5
Starch	30	30	30	30	30	30
Polyvinylpyrrolidone	7	7	7	7	7	7
Mg stearate	5	5	5	5	5	5
Percentage of Na lauryl-sulfate	0	0.86	2	3.4	5	7.53

Taking these formulations, the dissolution curve shown in FIG. 1 was plotted, the percentage of dissolved fenofibrate (Y) being given as a function of the percentage of sodium lauryl-sulfate contained in the formulation (X). The dissolution kinetics are determined, as specified in the European Pharmacopoeia, using a rotating-vane apparatus, the eluent consisting of water and 0.1M sodium lauryl-sulfate. The fenofibrate is determined by UV spectrophotometry at 282 nm. The curve in FIG. 1 is given by the values obtained after 20 minutes.

These results show that 82% of fenofibrate is dissolved at a sodium lauryl-sulfate concentration of 0%, 87% of fenofibrate is dissolved at a concentration of 0.5%, 92% of fenofibrate is dissolved at a concentration of 1% and a maximum dissolution of 95 to 96% of fenofibrate is obtained as from a sodium lauryl-sulfate concentration of 4%.

The dissolution curves were also plotted, in a continuous-flow cell with a flow rate of 20 ml/min of 0.1M sodium lauryl-sulfate, for formulations containing co-micronized fenofibrate and sodium lauryl-sulfate (NaLS), by comparison with micronized fenofibrate and with formulations obtained by intimately mixing separately micronized fenofibrate and lauryl-sulfate. The comparison is made by means of T 50%, i.e. the time required for 50% of the fenofibrate to dissolve. The results obtained are collated in Table II below:

TABLE II

VALUE OF THE T 50% TIMES (in minutes)			
INGREDIENTS	A	B	C
Micronized pure fenofibrate	37.165	37.165	0
Fenofibrate + 1% of NaLS	18.01	8.62	−52.14
Fenofibrate + 3% of NaLS	23.75	12.68	−46.61
Fenofibrate + 5% of NaLS	20.35	11.425	−43.86
Fenofibrate + 7% of NaLS	14.5	10.76	−25.79

Notes
A mixture of micronizates
B co-micronization of the mixture of ingredients
C variation $\frac{B-A}{A} \times 100$ (in %)

These results show that the T 50% of the fenofibrate is very significantly reduced (hence the dissolution rate of the fenofibrate is very significantly increased) when the fenofibrate and the sodium lauryl-sulfate are co-micronized, compared with the mixture of separately micronized fenofibrate and sodium lauryl-sulfate and compared with fenofibrate alone.

The dissolution rate of fenofibrate is correlated with the bioavailability of fenofibrate, which increases with the dissolution rate. The above results shown that it was not within the understanding of those skilled in the art to prepare a therapeutic composition characterized by the co-micronization of fenofibrate and a solid surfactant.

These results have been confirmed in clinical trials. Fenofibrate was administered to groups of healthy subjects, (a) in the form of a single administration (1 gelatin capsule) of 300 mg of non-micronized fenofibrate (marketed under the tradename "LIPANTHYL 300") and (b) in the form of a single administration of 200 mg of co-micronized fenofibrate obtained according to Preparation III described above. Blood samples are taken from the subjects at regular intervals and one of the active metabolites—2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropionic acid—is determined. The curve showing the concentration of this metabolite as a function of time is plotted and the area under the curve [AUC(O-∞)], expressed in mg/1.h, is calculated.

The results obtained are shown in Table III below:

TABLE III

BIOAVAILABILITY PARAMETER	FENOFIBRATE 200 mg (1)	FENOFIBRATE 300 mg (2)
AUC(0-∞)(mg/1.h)	174.15 ± 48.67	168.85 ± 57.68
C max (m/l)	10.86 ± 2.13	10.39 ± 2.89
t max (h)	5.97 ± 2.50	5.52 ± 1.70
t ½ (h)	15.13 ± 4.27	17.79 ± 8.77

Notes
(1) co-micronized fenofibrate (200 mg)
(2) non-micronized fenofibrate (300 mg)

The results in Table III show that there is not a statistically significant difference between the in vivo bioavailability of 200 mg of co-micronized fenofibrate according to the invention and 300 mg of non-micronized fenofibrate (which is currently the preferred dosage form for a single daily administration). In other words, co-micronized fenofibrate at a 200 mg dose is bioequivalent to non-micronized fenofibrate at a 300 mg dose.

According to another aspect of the invention, a method for improving the bioavailability of fenofibrate in vivo is recommended, the said method comprising co-micronization of the fenofibrate and a solid surfactant, the said co-micronization being carried out by

micronization of a fenofibrate/solid surfactant mixture until the particle size of the powder obtained is less than 15 μm and preferably less than or equal to 5 μm.

What is claimed is:

1. A therapeutic composition, which is presented in the form of gelatin capsules and which is useful especially in the oral treatment of hyperlipidemia and hypercholesterolemia, said composition containing a co-micronized mixture of particles of fenofibrate and a solid surfactant, wherein the mean particle size of said co-micronized mixture is less than 15 μm.

2. The therapeutic composition according to claim 1 wherein the weight ratio surfactant/fenofibrate is between about 0.75/100 and 10.5/100.

3. The therapeutic composition according to claim 1 wherein the amount of fenofibrate is equal to 200 mg per therapeutic unit.

4. The therapeutic composition according to claim 1, wherein the solid surfactant is sodium lauryl-sulfate.

5. The therapeutic composition according to claim 4, wherein the amount of sodium lauryl-sulfate is between 0.5 and 7% by weight, relative to the total weight of the formulation.

6. The therapeutic composition according to claim 1, wherein said mean particle size is less than or equal to 10 μm and said solid surfactant is sodium lauryl-sulfate.

7. The therapeutic composition according to claim 1, which also contains excipients such as dispersants, fillers and flow enhancers.

8. A method for the manufacture of a therapeutic composition according to claim 1, which comprises:

(i) intimately mixing and then co-micronizing the fenofibrate and a solid surfactant,

(ii) adding lactose and starch to the mixture obtained,

(iii) converting the whole to granules in the presence of water,

(iv) drying the granules until they contain no more than 1% of water,

(v) grading the granules,

(vi) adding polyvinylpyrrolidone and magnesium stearate, and

(vii) filling gelatin capsules.

9. The method according to claim 8, wherein the mean particle size of the co-micronized fenofibrate and sodium lauryl-sulfate is less than 15 μm.

10. A method for improving the bioavailability of fenofibrate in vivo, which comprises co-micronization of the fenofibrate and a solid surfactant, the said co-micronization being carried out by micronization of a fenofibrate/solid surfactant mixture until the particle size of the powder obtained is less than 15 μm.

11. A method for treatment of hyperlipidemia or hypercholesterolemia comprising orally administering the therapeutic composition of claim 6 to a patient.

12. The method of treatment of claim 11, wherein said particle size is less than or equal to 5 μm.

* * * * *

US006074670A

United States Patent [19]

Stamm et al.

[11] **Patent Number: 6,074,670**

[45] **Date of Patent: Jun. 13, 2000**

[54] **FENOFIBRATE PHARMACEUTICAL COMPOSITION HAVING HIGH BIOAVAILABILITY AND METHOD FOR PREPARING IT**

[75] Inventors: **André Stamm**, Griesheim, France; **Pawan Seth**, Irvine, Calif.

[73] Assignee: **Laboratoires Fournier, S.A.**, Dijon, France

[21] Appl. No.: **09/005,128**

[22] Filed: **Jan. 9, 1998**

[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[7] **A61K 9/16**; A61K 9/20; A61K 9/50

[52] **U.S. Cl.** **424/462**; 424/456; 424/458; 424/459; 424/489; 424/490; 424/497; 424/464; 424/465; 424/469; 424/470

[58] **Field of Search** 424/465, 464, 424/470, 472, 479, 482, 489, 2.15, 451, 456, 458, 462, 490, 497

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Primary Examiner—Thurman K. Page
Assistant Examiner—Brian K. Seidleck
Attorney, Agent, or Firm—Hale and Dorr LLP

[57] **ABSTRACT**

The invention provides an immediate-release fenofibrate composition comprising (a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 μm, a hydrophilic polymer and, optionally, a surfactant, the polymer making up at least 20% by weight of (a); and (b) optionally one or several outer phase(s) or layers(s). The invention also provides a method for preparing said composition.

38 Claims, 2 Drawing Sheets

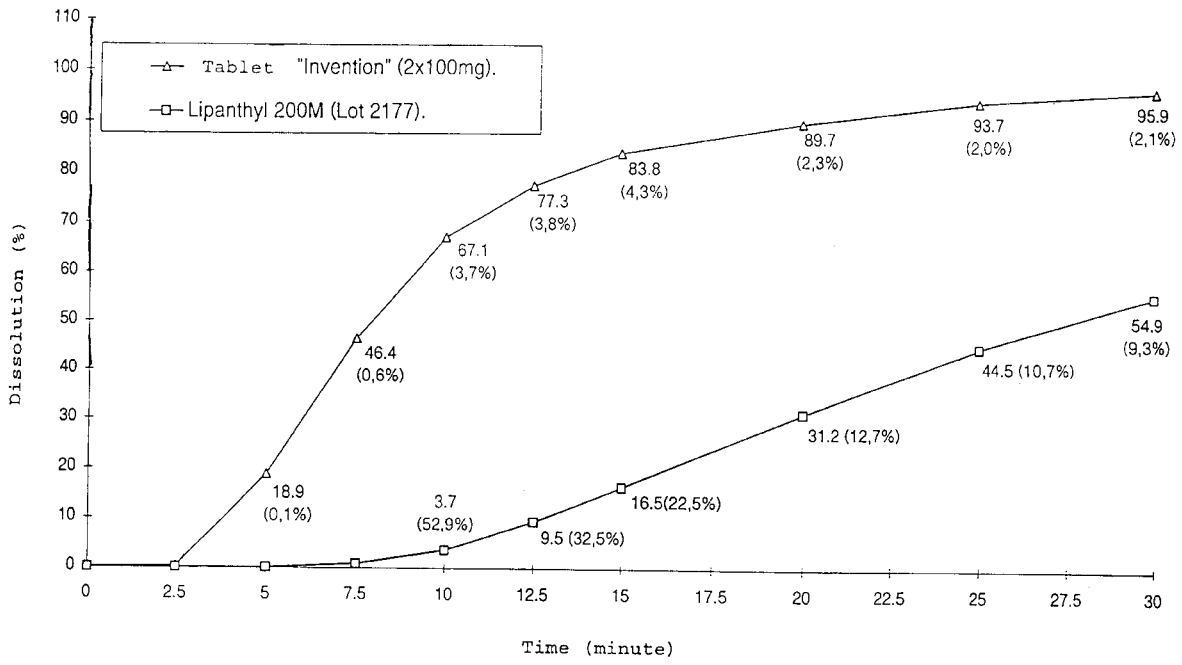
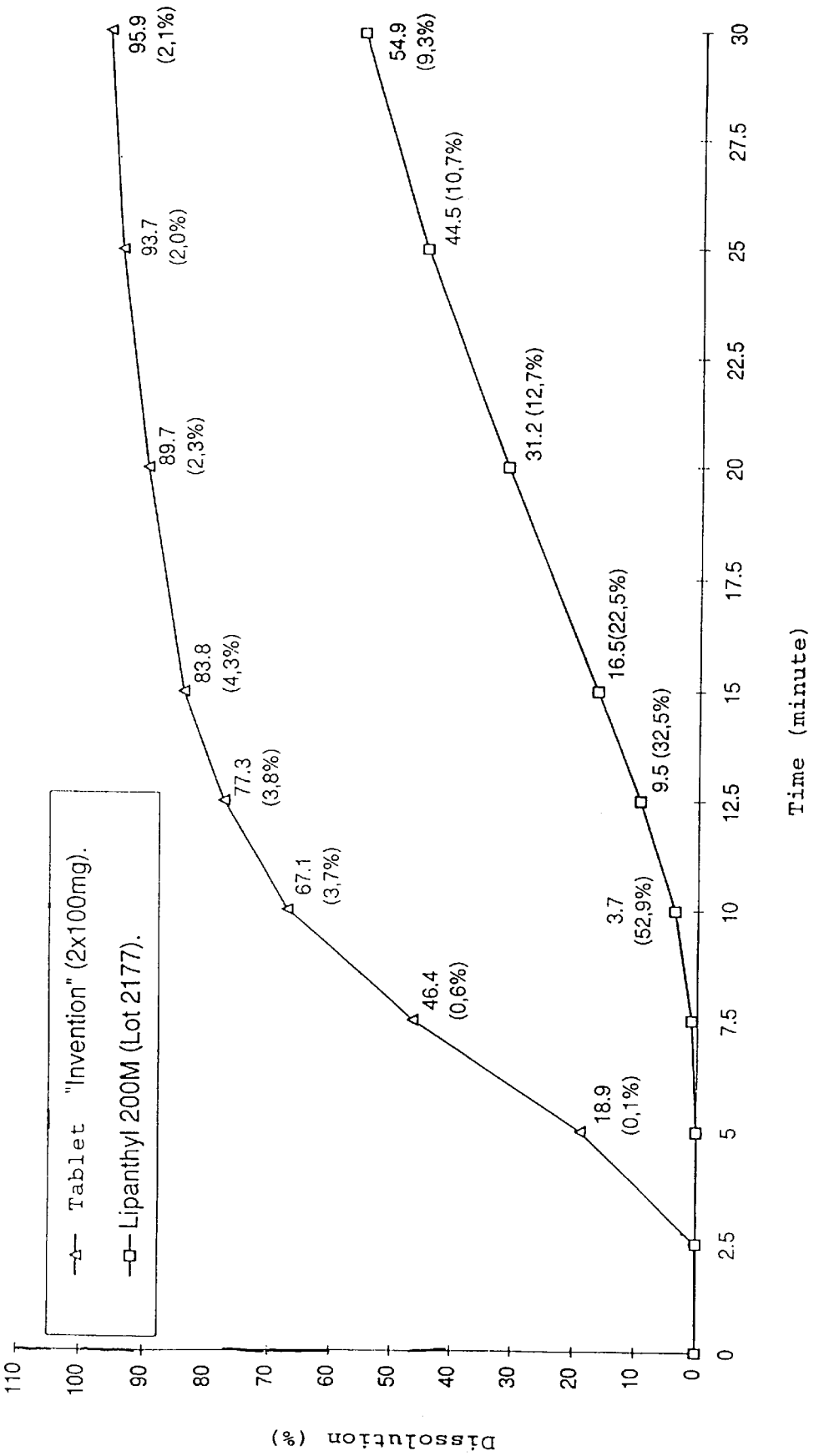


FIG 1


Tablet "Invention" (2x100mg).
Lipanthyl 200M (Lot 2177).
Dissolution (%)
Time (minute)
0
10
20
30
40
50
60
70
80
90
100
110
0
2.5
5
7.5
10
12.5
15
17.5
20
22.5
25
27.5
30
95.9 (2,1%)
93.7 (2,0%)
89.7 (2,3%)
83.8 (4,3%)
77.3 (3,8%)
67.1 (3,7%)
46.4 (0,6%)
18.9 (0,1%)
54.9 (9,3%)
44.5 (10,7%)
31.2 (12,7%)
16.5(22,5%)
9.5 (32,5%)
3.7 (52,9%)

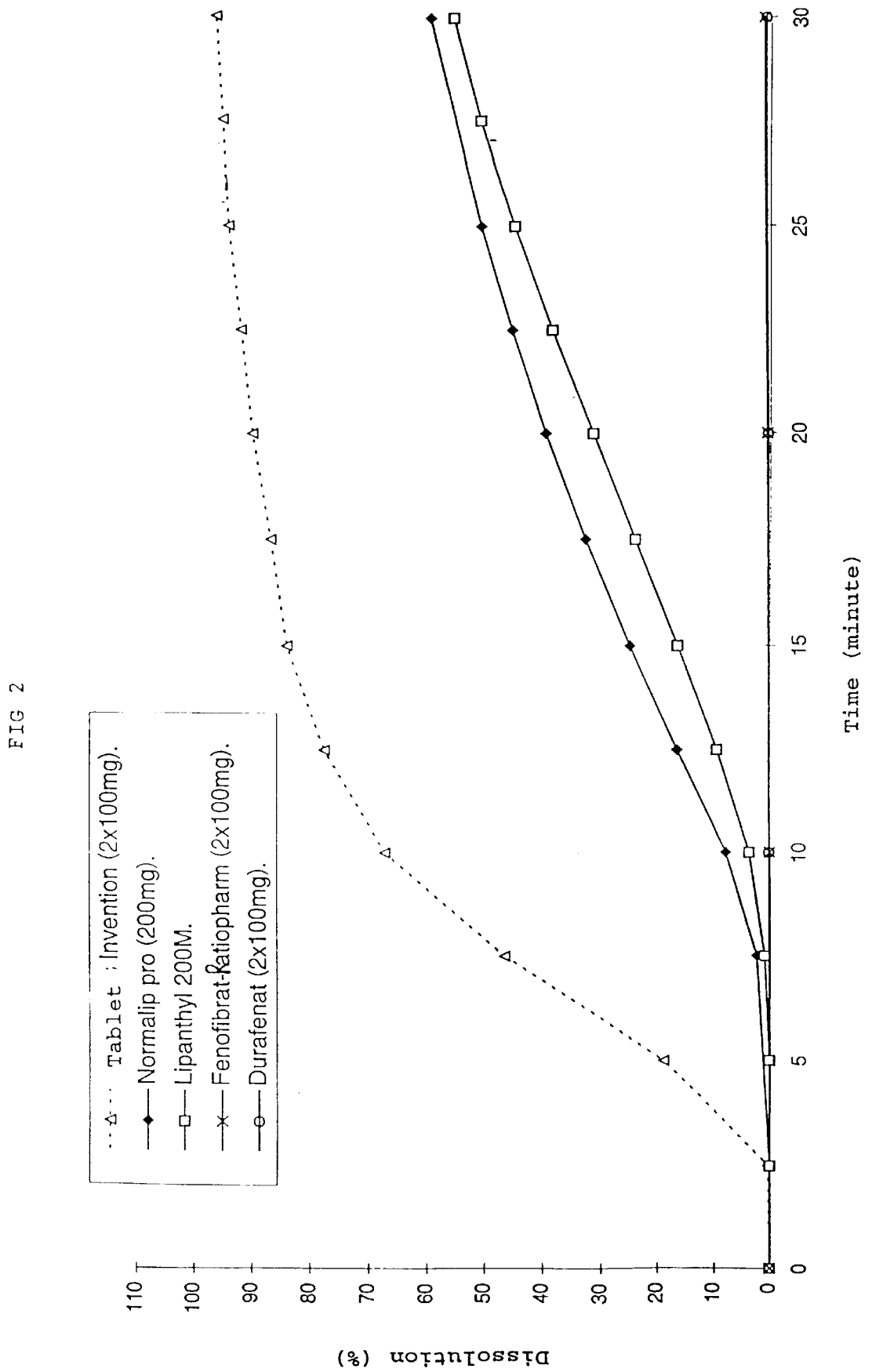

Tablet : Invention (2x100mg).
Normalip pro (200mg).
Lipanthyl 200M.
Fenofibrat-Ratiopharm (2x100mg).
Durafenat (2x100mg).
Dissolution (%)
110
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
Time (minute)

FIG 2

FENOFIBRATE PHARMACEUTICAL COMPOSITION HAVING HIGH BIOAVAILABILITY AND METHOD FOR PREPARING IT

BACKGROUND OF THE INVENTION

The present invention relates to a novel pharmaceutical composition having high bioavailability through improved dissolution, and a method for preparing it. The invention more particularly relates to a pharmaceutical composition for administration by oral route, containing an active ingredient of poor aqueous solubility.

Numerous active ingredients suffer from the disadvantage of being poorly soluble in an aqueous medium, thus having an insufficient dissolution profile and, consequently, poor bioavailability within the organism, following oral administration. The therapeutic dose required to be administered must thus be increased in order to obviate this disadvantage. This particularly applies to numerous hypolipemiant active ingredients, such as those belonging to the fibrate family.

Fenofibrate is a well-known hypolipemiant from the family of fibrates, which is commercially available in various doses (100 and 300 mg for example Secalip®) but in a form leading to poor bioavailability of the active ingredient. Indeed, due to it poor hydrosolubility, fenofibrate is poorly absorbed in the digestive tract and consequently its bioavailability is incomplete, irregular and often varies from one person to another.

To improve the dissolution profile of fenofibrate and its bioavailability, thereby reducing the dose requiring to be administered, it would be useful to increase its dissolution so that it could attain a level close to 100%.

Moreover, for patient comfort, it is advantageous to seek a dosage form that only requires the medicament to be taken once daily while giving the same effect as one administered several times daily.

EP-A-0330532 discloses a method for improving bioavailability of fenofibrate. This patent describes the effect of co-micronizing fenofibrate with a surfactant, for example sodium laurylsulfate in order to improve fenofibrate solubility and thereby increase its bioavailability. This patent teaches that co-micronizing fenofibrate with a solid surfactant improves fenofibrate bioavailability to a much greater extent than the improvement that would be obtained either by adding a surfactant, or through solely micronizing the fenofibrate, or, yet again, through intimately mixing the fenofibrate and surfactant, micronized separately. The dissolution method employed is the conventional rotating blade technique (European Pharmacopoeia): product dissolution kinetics are measured in a fixed volume of the dissolution medium, agitated by means of a standardized device; a test was also carried out with an alternative technique to the European Pharmacopoeia, using the continuous-flow cell method.

The process of EP-A-0330532 leads to a new dosage form in which the active ingredient, co-micronized with a solid surfactant, has improved fenofibrate dissolution, and thus increased bioavailability, which makes it possible, for a given level of effectiveness, to decrease the daily dose of the medicament: respective 67 mg and 200 mg instead of 100 mg and 300 mg.

However, the preparation method in that patent is not completely satisfactory inasmuch as it does not lead to complete bioavailability of the active ingredient, and suffers from several disadvantages. The technique of co-micronizing fenofibrate with a solid surfactant does, it is true, improve dissolution of the active ingredient, but this dissolution remains, however, incomplete.

There is thus a need to improve fenofibrate bioavailability in order to attain, over very short periods of time, a level close to 100% (or, in any case, better than the following limits: 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes in a medium consisting of 1200 ml water to which 2% Polysorbate 80 is added, or of 1000 ml of water to which 0.025M sodium lauryl sulfate sodium is added, with a blade rotation speed of 75 rpm), and this even when dissolution media having a low surfactant content are used.

Applicant has found that, surprisingly, it is possible to resolve this problem by a new method for preparing a pharmaceutical composition by spraying a suspension of the active ingredient onto an inert hydrosoluble carrier. The present invention also relates to pharmaceutical compositions thus prepared.

The use is already known of a polymer, such as polyvinylpyrrolidone for producing tablets, in concentrations of the order of 0.5 to 5% by weight, at a maximum 10% by weight. In this case, the polyvinylpyrrolidone is used as a binder. Similarly, the use of a polymer such as hydroxymethylpropylmethyl cellulose as a granulation binder is known. Thus, European patent application 0,519,144 discloses pellets of a poorly soluble substance, omeprazole, obtained by spraying a dispersion or suspension of the active ingredient in a solution containing said polymer onto inert pellets in a fluidized-bed granulator. However, here again, the polymer (HPMC and HPC) is only used as a granulation binder, in an amount of about 50% by weight, based on the weight of the active ingredient, which, bearing in mind the presence of the inert pellets of a large size (about 700 μm) and the overall final weight leads to final active ingredient and polymer contents which are very low, of the order of barely a few percent based on the weight of the final covered pellet. Finally, it will be noted that the size of the inert pellets in this documents is fairly large, which, in the case of fenofibrate, would lead to a final formulation having a volume which is much too large for ready oral administration.

The use of polymer, such as polyvinylpyrrolidone for manufacturing "solid dispersions" is also known, obtained in general by co-precipitation, co-fusion or liquid-phase mixing followed by drying. What we have here is fixation of the active ingredient in isolated microparticles on the polyvinylpyrrolidone, which avoids problems of poor wetting of the solid and re-agglomeration of the particles. The article "Stable Solid Dispersion System Against Humidity" by Kuchiki et al., Yakuzaigaku, 44 No. 1, 31–37 (1984) describes such a technique for preparing solid dispersions using polyvinylpyrrolidone. The amounts of PVP here are very high, and the ratio between the active ingredient and PVP are comprised between 1/1 and 1/20. In the case however there is no inert carrier.

WO-A-96 01621 further discloses a sustained release composition, comprising an inert core (silica in all examples) coated with a layer which contains the active ingredient in admixture with a hydrophilic polymer, the weight ratio active ingredient/polymer being comprised between 10/1 and 1/2 and the weight ratio active ingredient/inert core being comprised between 5/1 and 1/2, with an outer layer to impart the sustained release property. These compositions can be compressed. The hydrophilic polymer can be polyvinylpyrrolidone. This document also discloses a